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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,718	10/03/2005	Philip John Blower	CARPMAELS.00101	2261

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 07/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/526,718	BLOWER ET AL.	
	Examiner	Art Unit	
	Christina Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *10-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/01/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

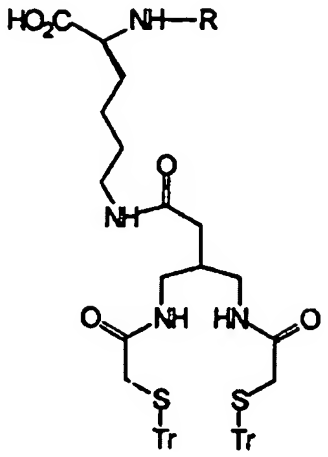
1. Applicant's election of Group I (claims 1-9) and the species comprising lysine, Fmoc and Boc-hynic in the reply filed on 06/29/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-9 are pending; claims 10-13 are withdrawn from consideration for pertaining to a non-elected invention.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1 and 5-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Hunter and Luyt (*J. Labeled Compds. Radiopharm.*, **2000**, *43*, 403). Hunter and Luyt teach the following chelator-derivatised amino acid:



1 R = CBZ

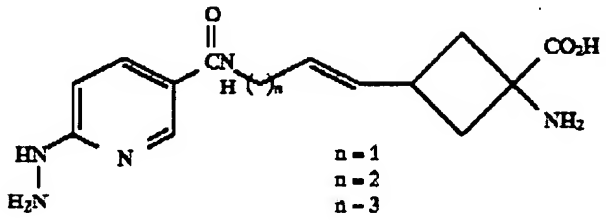
2 R = Fmoc

4. With respect to claim 1, the compound taught by Hunter and Luyt comprises a protected primary amino group (the CBZ- or Fmoc-protected backbone amino group of the amino acid), a carboxylic acid group and a chelator group capable of binding a metallic radionuclide (the N-hydroxysuccimidyl group containing a N_2S_2 core which, as stated by Hunter and Luyt, chelates technetium-99m and rhenium). The thiols are protected in the compound above. Hunter and Luyt note that deprotection of the thiols will yield a N_2S_2 conjugate that is ready for rhenium or technetium chelation. See page 404.

5. The chelator-derivatised amino acid taught by Hunter and Luyt meets the further limitation of claims 5-7 in that the amine and carboxylic acid groups are embodied in the amino acid L-lysine.

6. The chelator-derivatised amino acid taught by Hunter and Luyt meets the further limitation of claims 8 and 9 in that the amino group is protected and can be protected by Fmoc.

7. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Goodman and Shoup (USPN 5,817,776). Goodman and Shoup teach the following chelator-derivatised amino acid wherein the chelator group is hynic:



See example 28, columns 44-49. With respect to claim1, the compound above is a derivatized amino acid comprising a primary amino group, a carboxylic acid group, and a chelator group capable of binding to a radionuclide. The chelator group is hynic which can coordinate technetium-99m.

The chelator-derivatised amino acid taught by Goodman and Shoup meets the further limitation of claims 3 and 4 in that the hydrazine of the hynic group can be protected, specifically with Boc (see bottom of column 47).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

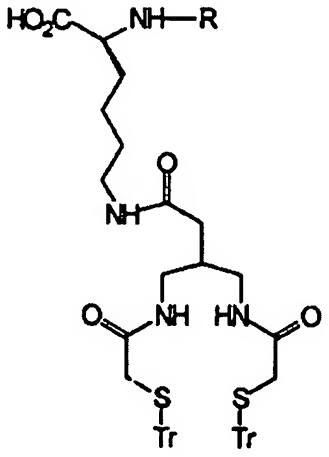
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunter and Luyt (*J. Labeled Compds. Radiopharm.*, **2000**, *43*, 403) in view of Graham *et al.* (*Tet. Let.*, **2002**, *43*, 5021) and Babich *et al.* (*J. Nuc. Med*, **1993**, *34*, 1964, citation number 2 on the Information Disclosure Statement of 06/01/2005).

10. As noted above, Hunter and Luyt teach the following chelator-derivatised amino acid:



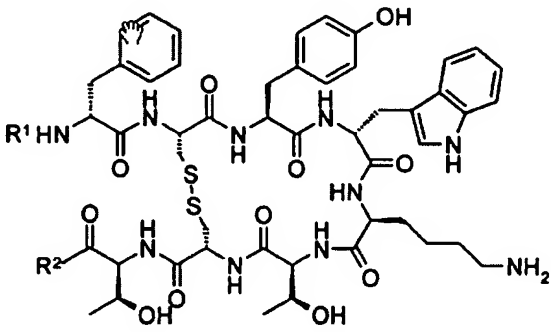
1 R = CBZ

2 R = Fmoc

With respect to claim 1, the compound taught by Hunter and Luyt comprises a protected primary amino group (the CBZ- or Fmoc-protected backbone amino group of the amino acid), a carboxylic acid group and a chelator group capable of binding a metallic radionuclide (the N-hydroxysuccimidyl group containing a N_2S_2 core which, as stated by Hunter and Luyt, chelates technetium-99m and rhenium). The thiols are protected in the compound above. Hunter and Luyt note that deprotection of the thiols will yield a N_2S_2 conjugate that is ready for rhenium or technetium chelation. See page 404.

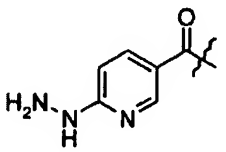
11. Hunter and Luyt do not teach that the chelator group can be HYNIC.

12. Graham *et al.* teach a method for solid-phase peptide synthesis via the Fmoc strategy that allows the functionalization of both the C- and N-terminals of a peptide with HYNIC. The peptides synthesized by Graham *et al.* include:



2 R^1 = H, R^2 = $NHCH_2CH_2NH$-HYNIC

4 R^1 = HYNIC, R^2 = OH



HYNIC

In each peptide, the HYNIC group is attached to the peptide via a free amino group. With respect to claims 3 and 4, the HYNIC reagent used in the synthesis of these peptides included a protected hydrazine group. Specifically, the hydrazine group was protected with Boc (6-(2'-*tert*-butoxycarbonylhydrazino)nicotinic acid or Boc-HYNIC, see page 5021, column 2).

Babich *et al.* teach the coupling of hynic to lysines in chemotactic peptide analogs using Boc-hynic (hydrazine protection) as a reagent following solid phase synthesis of the peptide (see page 1965, column 1).

13. It would have been obvious to one of ordinary skill in the art to combine the Boc-HYNIC chelator group taught by Graham *et al.* and Babich *et al.* and the chelator-derivatised amino acid

taught by Hunter and Luyt to make N-α-Fmoc-N-ε-(Hynic-Boc)-Lysine as shown in Figure 1 of the instant application.

14. The skilled artisan would have been motivated to do so given the teachings of Hunter and Luyt. The authors note that radiolabeling peptides with technetium-99m is a method to achieve target-specific imaging agents. Hunter and Luyt further note that the most practical method to create such peptides is the indirect labeling method, where a bifunctional chelator is attached to a peptide followed by ^{99m}Tc labeling. The problem with this method however, is that if a peptide contains more than one nucleophilic site, attachment a chelator may occur at random or at multiple locations (as in the method utilized by Babich *et al.*). This disadvantage is circumvented by the method of Hunter and Luyt in which a peptide is synthesized by solid-phase chemistry using a lysine with a bifunctional chelator already attached. Upon chelation, the resulting ^{99m}Tc complex will exist in a pre-defined location in the peptide. In addition, the chelation site will be situated away from the peptide backbone. Hunter and Luyt demonstrate the effectiveness of this method using the a chelator other than HYNIC. Graham *et al.* note that HYNIC is an appropriate chelator for radiolabels that can diagnose and treat certain tumors. In particular HYNIC-D-Phe^1-Tyr^3-octreaotide labeled with ^{99m}Tc for single photon emission tomography is an effective tool for nuclear medicine. Graham *et al.* demonstrate that the hynic group can be specifically incorporated into a peptide at either of the termini. The substitution of HYNIC into the chelator-derivatised amino acid taught by Hunter and Luyt would allow for the site-specific incorporation of this effective group into a wide-variety of peptides used to target tumors and receptors. The effectiveness of peptides with hynic-derivatized lysines is demonstrated by Babich *et al.*

15. There would have been a reasonable expectation of success given that the chemistry employed by Graham *et al.* and Babich *et al.* to couple HYNIC to the peptide involves attaching the group to a free amine. This chemistry is analogous to that which would have to be performed to couple HYNIC to the side chain amino group of lysine.

16. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Cheng *et al.* (*J. Am. Chem. Soc.*, **1996**, *118*, 11349); and Kazmierski (*Tet. Let.*, **1993**, *34*, 4493).

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Bradley whose telephone number is (571) 272-9044. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M.

19. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

20. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

cmb

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